GUIDANCE[1]

DILTIAZEM HYDROCHLORIDE TABLETS

IN VIVO BIOEQUIVALENCE

AND *IN VITRO* DISSOLUTION

I. INTRODUCTION

A. Clinical Usage

DiltIazem HCl is classified as a cardiovascular preparation and antianginal calcium channel blocker. It is currently approved for i) angina pectoris due to coronary artery spasm and ii) chronic stable angina (classic effort-associated angina). Its therapeutic effects are brought about by its ability to block calcium entry into cardiac and vascular smooth muscle cells. It is known to dilate coronary arteries as well as increase the tolerance of angina sufferers to physical exertion by reducing the demand for myocardial oxygen(1).

The dosage is adjusted according to the needs of adult patients. The starting regimen of 30 mg four times daily is increased gradually till the optimum response is achieved with safety. Safety and efficacy of diltiazem is not established for pediatric use. Diltiazem is prescribed to a pregnant woman only if the potential benefit justifies any potential risk to the fetus. A nursing mother taking diltiazem should not breast-feed her infant.

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[1] This statement, prepared by the Division of Bioequivalence in the Office of Generic Drugs, is an informal communication under 21 CFR 10.90(b)(9) that represents the best judgment of the Division at this time. This statement does not necessarily represent the formal position of the Center for Drug Evaluation and Research, Food and Drug Administration, and does not bind or otherwise obligate the Center for Drug Evaluation and Research, Food and Drug Administration, to the views expressed. For further information about this guidance, contact the Division of Bioequivalence, Office of Generic Drugs, 7500 Standish Place, Metro Park North, Rockville, MD 20855 (Phone: 301-295-8290; Fax: 301-295-8183).

The most commonly observed adverse reactions are edema, headache, nausea, dizziness, rash and asthenia (weakness, lethargy).

Marion Laboratories is the innovator and markets this drug under the brand name i) Cardizem [R] in 30 mg, 60 mg, 90 mg and 120 mg strength (immediate release) tablets; ii) Cardizem [R] SR in 60 mg, 90 mg, and 120 mg strength extended-release capsules; and iii) Cardizem [R] CD in 180 mg, 240 mg, and 300 mg strength extended-release capsules.

B. Chemistry [1]

Diltiazem is 1,5-benzothiazepin-4(5H)one, 3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2, 3-dihydro-2(4-methoxyphenyl)-, monohydrochloride. The marketed product is a 2S,3S optical isomer(15). It is soluble in water (56.6 gm/ml), has a molecular weight of 450.9, a pKa of 7.7 (pH of 1% aqueous solution = 4.8) and an optical rotation of $[\alpha]_D = +117.8^{o}$. The structural formula of diltiazem HCl and its major metabolic pathways appears in the following figure:

DILTIAZEM HCl AND MAJOR METABOLIC PATHWAYS

C. Pharmacokinetics

After oral administration of diltiazem , 80-90% of th e dose is absorbed (1,3). Diltiazem undergoes extensive first pass metabolism and has 40-44% oral bioavailabilit y (1). Diltiazem is 70-80% bound to plasma protein s (1,2,8). Peak plasma diltiazem level is reached within 2 to 3 hours (1,7) after a single oral dose. Eliminatio n half-lives of 3 to 5 hours (1,7) and 5 to 9 hours (8,9) have been reported for diltiazem. Diltiazem i s metabolized by three major pathways into variou s

metabolites (12). These pathways are i) O-deacetylation, ii) N-demethylation and iii) O-demethylation (12). Desacetyldiltiazem (DAD) and N-monodemethyldiltiazem (NMD) are active metabolites (6,7,8,9,10).

Until 1987, the measurement of desacetyldiltiazem (DAD) and N-monodemethyldiltiazem (NMD) was found to be difficult in single (IV and oral) dose studies (4,5,6,10). However, in 1989, Boyd, et al (8) showed the possibility of measuring DAD and NMD following a single oral dose.

At one time, DAD was thought to be the major metabolite of diltiazem (2). It is 40-50% active compared to the parent compound (8,9,10) and shows on average only 20% of the plasma levels produced by diltiazem (6,7,8). DAD is 68% bound to plasma proteins (8). Following a single oral dose, average half lives of 7.5 hours and 19.5 hours (8) have been reported.

Recent studies have demonstrated that N-monodemethylation, leading to the formation of NMD (which is less active than DAD) is the major metabolic pathway. Average plasma levels of NMD are about 40% of those of diltiazem (6,7). NMD is 77% bound to plasma proteins and has an average half life of 8-10 hours (7,8).

Diltiazem HCl has a therapeutic concentration range of 50-200 ng/ml and is toxic above 1200 ng/ml (1,11).

II. BIOEQUIVALENCE STUDIES

A. Types of Studies Required

Diltiazem HCl, which is currently marketed as 30 mg, 60 mg, 90 mg, and 120 mg (immediate-release) tablets under the brand name Cardizem® by Marion, should be used as the reference drug product. The bioequivalence requirements for generic diltiazem HCl tablets are as follows:

1. A single-dose, fasting, two-way crossover study with the 120 mg strength generic diltiazem HCl test product compared to the reference product, Cardizem® 120 mg tablets.

2. *In vitro* dissolution testing of the 120 mg strength tablets from test and reference lots used in the *in vivo* bioequivalence study.

3. A generic firm may request a waiver of the bioequivalence study requirements for the 30 mg, 60 mg, and 90 mg strength tablets. The request for a waiver may be granted if the following conditions are met:

   a. The bioequivalence study on 120 mg tablet is acceptable.

   b. The 30 mg, 60 mg, and 90 mg tablets have formulations proportionally similar to 120 mg tablet.

   c. The 30 mg, 60 mg, and 90 mg tablets meet established *in vitro* dissolution specification(s).

B. Fasting Study

Objective: To objective of this study is to compare the bioavailability of a generic 120 mg diltiazem HCl tablet (test product) with that of the reference product Cardizem[R] 120 mg tablet under fasting conditions.

Design: The study design is a single dose, two treatment, two period, two sequence crossover with a washout period of at least 7 days. Subjects should be randomly assigned to the two possible dosing sequences.

Facilities: The clinical and analytical sites for the study should be given along with the names, titles and the curriculum vitae of the medical, scientific and analytical directors. The starting and ending dates for each clinical study period should be stated. The study protocols should be approved by an institutional review board, and informed consent forms should be signed by all participants.

Subjects: A minimum of 24 subjects should be enrolled in the study. It is the responsibility of the sponsor to recruit a sufficient number of subjects that will ensure adequate statistical power. Thus, the sponsor may recruit some replacement subjects in case of dropouts.

Subjects should be adult male volunteers between 18-45 years of age and within $\pm$10% of ideal body weight for body frame and height according to the Metropolitan Insurance Company Bulletin, 1983. All subjects should be

given a physical examination and appropriate laboratory tests 4 weeks prior to the initiation of the study . These should be repeated at the end of the study. Each subject must sign a written informed consent form.

Exclusion Criteria: Subjects should be excluded from th e study using the following and any other criteria deemed essential by the medical director of the study:

1. History of past or recent alco hol or drug addiction or abuse.

2. History of hypersensitivity to the drug product or related chemicals.

3. Exposure to known hepatic enzyme inducing o r inhibiting agents(s) within 30 days prior to th e study.

4. Use of any prescription drug p roduct within 2 weeks and any OTC drug product withi n 3 days prior to the study.

5. Participation in an investigational drug stud y within 30 days prior to the study.

6. Blood donation within 30 days prior to the study.

7. Tobacco use in any form.

Procedures: After an overnight (at least 10 hours) fast , subjects should receive a single dose of the test produc t or the reference product with 240 ml of water:

Treatment A: Test product, 1 x 120 mg, diltiaze m tablet.

Treatment B: Reference product, 1 x 120 mg Cardizem ^{R} tablet (Marion).

The test product should be fro m a production lot or from a lot produced under production conditions. The lot siz e of the test product should be equal to or more tha n 100,000. The lot numbers of b oth the test and reference products and the expiration date for the referenc e product should be stated. The potency of the reference product should not differ from that of the test product by more than $\pm$5%. The sponsor should include a statemen t

of the composition of the test product.

The clinical staff administeri ng the doses should verify that the dose was ingested by each subject. At leas t seven days after the last samp le collection in the first period of the study, each subject should receive th e alternative treatment.

Restrictions: Prior to and during each study period , subjects should conform to the following restrictions:

a. Water will be allowed ad libitum except for on e hour before and after drug administration.

b. Subjects should be served standardized meals n o less than 4 hours after drug administration. Only standardized meals and beverag es at specified times will be allowed during the study.

c. No alcohol or xanthine-containing foods o r beverages should be consumed for 48 hours prior to each study period and until after the last bloo d sample is collected.

d. Subjects will be confined to the clinical facility for 48 hours after each dosing.

Blood Sampling: Blood samples should be drawn at 0 (predose), 0.5, 1.0, 1.5, 2, 3 , 4, 6, 8, 10, 12, 14, 16, 24, 30, 36 and 48 hours postdo se. The samples should be cooled immediately on ice and the plasma should b e separated and frozen within on e hour of collection. The separated plasma should be stored frozen (not more than six weeks) at -20 ^{o} C until assayed. Sponsor sh ould state the elapsed time between sample collection and sampl e assay for every subject. Sponsor should avoid thawin g and refreezing of samples. An explanation should be give n for any missing samples.

Analytical Methods: There are HPLC methods available to measure diltiazem and its major metabolites (DAD and NMD) (13, 14). The firm may develop its own assay for th e measurements of diltiazem and its metabolites (DAD an d NMD).

The assay should be properly validated for:

1. accuracy (determined by % of the nominal),

2. inter- and intra-day precision (determined by % CV of standards used in a calibration curve and quality control (QC) standards),

3. specificity (no interference by other analytes),

4. limit of quantitation and

5. stability data (see below).

The lowest concentration of a standard on the calibration curve should be the limit of quantitation. The QC standards (low, middle and high ranges of the calibration curve) should be prepared on the same day as the collection of subject samples and should be stored with the subject samples under the same conditions. The sponsor should measure the analytes from all plasma sample of a subject from both treatments in the same run along with the calibration curve standards and QC standards.

The sponsor should submit the following assay validation data:

1. Complete prestudy assay validation data and the details of analytical method.

2. Raw data, equation used for plotting the calibration curve, internal standard, and a summary table showing all the values for standards of calibration curves and QC-standards obtained from the number of calibration curves employed in the study with mean value and % CV for every standard in calibration curves and QC-standard.

3. Stability data from study conducted at:

   a. frozen conditions for at least as long as the longest period of time between sample collection and sample assay for the study,

   b. room temperature for at least as long as the longest period of time between sample thawing and sample assay, and

   c. freeze-thaw cycles if reassay is anticipated.

The sponsor should state in standard operating procedures

the analytical criteria which determine the acceptability of a standard curve. A table for reassay should include a list of reassayed samples, original concentration, reason for reassay, reassay concentration, reported concentration and reason for selection of reported concentration.

Pharmacokinetic Analysis: The individual subject plasma drug (and metabolites) concentration-time profiles and the mean profiles for two treatments should be presented (separately) in tabular forms. From individual plasma profile(s) the following pharmacokinetic parameters should be obtained. The individual and mean values for both treatments should be presented:

a. AUC_{0-t}, where T is the last measurable time point calculated by the trapezoidal rule.

b. $AUC_{0-\infty}$, where $AUC_{0-\infty} = AUC_t + C_t/(\lambda_z)$, C_t is the last measurable drug concentration and λ_z is the terminal elimination rate constant.

c. The terminal phase elimination rate constant (λ_z) is calculated using an appropriate pharmacokinetic method.

d. Peak drug concentration (C_{max}) and the time to peak drug concentration (T_{max}) are obtained directly from the data without interpolation.

Statistical Analysis: The sponsor should perform the following tests:

a. Analysis of variance (ANOVA) appropriate for a crossover design on the pharmacokinetic parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} using General Linear Models (GLM) procedure of SAS(12) or an equivalent program should be performed. The statistical model should include terms describing the error attributable to sequence [subj (seq)], period and treatment. The sequence effect should be tested against the between subject [subj (seq)] error term. All other main effects should be tested against the residual error from the ANOVA.

b. The ESTIMATE statement in SAS should be used to obtain linear estimates for the adjusted differences between treatment means and the error associated with these differences.

c. The LSMEANS statement should be used to calculate least-square means for treatments.

d. The two one-sided tests procedure (13) should be used to calculate 90% confidence intervals for the mean difference for AUC and C_{max}, which should generally be within $\pm$ 20% of the corresponding reference mean.

Pharmacodynamic Measurements: Diltiazem is known to cause PR interval prolongation in healthy subjects after a single oral dose (8). The sponsor should perform ECG measurements on every subject at predose and at 2, 3, and 4 hours postdose to measure a possible PR interval prolongation due to the treatments. The results of these measurements should be submitted in the final report.

Adverse Reactions: The sponsor should report all adverse reactions that occurred during the study with regard to the nature, onset, duration, frequency, severity, type of treatment during which the reaction occurred and the suspected relation to the drug treatment.

III. DISSOLUTION TESTING

Dissolution testing should be conducted on 12 individual dosage units of the test and reference products from the same lots used in the *in vivo* bioequivalence studies using the following methodology:

Apparatus:	USP XXII apparatus II (paddle)
RPM:	75
Medium:	900 ml distilled or deaerated water at 37 °C
Tablets:	12
Ref. Drugs:	Cardizem® from Marion
Sampling time:	30, 60, 90 and 180 minutes
Specification:	NMT 60% of the labeled amount of the drug in the dosage form is dissolved in 30 minutes and NLT 85% of the labeled amount of the drug in the dosage form is dissolved in 180 minutes.

The sponsor should include the following information from the dissolution testing:

a. Lot numbers for both test and reference products.

b. The percent dissolution for each dosage unit being tested

at each time interval.

c. The mean percent dissolved, the range of percent dissolution and the coefficient of variation for the 12 units being tested at each time interval.

d. Validation data for the analytical method used.

e. Expiration date for the reference product.

IV. WAIVER REQUESTS

A sponsor may request a waiver of the bioequivalence study requirements for immediate release 30 mg, 60 mg, and 90 mg diltiazem tablets. The sponsor should include the following information with the waiver request:

1. A side-by-side comparison of the composition of the 120 mg tablet and the lower strength tablet which is the subject of the waiver request.

2. Comparative (test and reference) dissolution data for lower strength tablets.

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